Movement Disorders
CLINICAL PRACTICE

Is it Useful to Classify PSP and CBD as Different Disorders? Yes

Helen Ling, MRCP, PhD,[1,*] and Antonella Macerollo, MD[2]

Background

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are sporadic adult onset neurodegenerative conditions that are closely related with notable overlap in their clinical presentations, pathological features, biochemistry, and genetic risk factors. The definitive diagnosis of PSP and CBD can only be confirmed at postmortem, as there is currently no reliable distinctive feature for definitive antemortem diagnosis.

The terms PSP and CBD were traditionally used to describe both their classic clinical phenotypes and pathological diagnosis. The classic and most common presentation of PSP pathology is a symmetrical, akinetic-rigid syndrome with early postural instability and vertical supranuclear palsy.[1] Clinico-pathological studies have since identified other clinical phenotypes associated with PSP pathology.[2–4] For clarity, the classic presentation is now referred to as Richardson's syndrome (RS) and to denote their postmortem confirmed PSP pathology, such cases are labelled as PSP-RS.[4] The classic clinical syndrome of CBD is the presentation of an apraxic, dystonic, and rigid limb with asymmetrical cortical signs and distal myoclonus known as corticobasal syndrome (CBS).[5] Autopsy series have shown that CBS may not be the most common presentation of CBD, and the term CBD-CBS is reserved for CBD cases with CBS clinical presentation.[6]

In view of the phenotypic heterogeneity of PSP and CBD, it can be difficult for clinicians to predict the underlying pathology. Nevertheless, accurate documentation of clinical features continues to be essential and informative in providing clues to the underlying pathological processes. Longitudinal data on the temporal evolution of clinical features along with postmortem findings have permitted the delineation of the existing and emerging phenotypes of PSP and CBD in clinicopathological series. "Lumping" clinical features by describing them with non-specific diagnostic categories such as PSP mimics, PSP-plus, and atypical parkinsonism will preclude future advances in understanding the underlying mechanisms of these distinct pathological processes.

The aim of this article is to demonstrate that PSP and CBD are two different disorders and therefore they should be classified as such. In this article, the terms PSP and CBD refer to the pathological entities.

Characteristic Neuropathological Features

Pathologically, both PSP and CBD have neuronal and glial lesions that are composed primarily of hyper-phosphorylated tau. Nevertheless, the overall patterns of distribution of neuronal and glial lesions differ.[7] In general, cortical and white matter are more affected in CBD, while deep gray matter regions are more affected in PSP. PSP and CBD have their own validated neuropathological diagnostic criteria and are considered as distinct pathological entities.[8,9]

Macroscopically, depigmentation of the substantia nigra is a shared feature. Atrophy of the subthalamic nucleus, superior cerebellar peduncle, and hilum of the cerebellar dentate nucleus are observed in PSP. Many CBD cases have asymmetrical atrophy of parasagittal regions of superior frontal gyrus and superior parietal lobule, affecting pre- and post-central gyri. The cerebral white matter adjacent to the atrophic cortical areas is frequently attenuated with a gray discoloration. Atrophy of the corpus callosum is another common feature.

Microscopically, globose neurofibrillary tangles (NFTs) are the typical neuronal tau lesions in PSP, while pretangles are the most common neuronal lesions in CBD and well-formed NFTs are rare. Thread-like processes in white matter are particularly numerous in CBD, distinguishing it from PSP. In PSP, tau accumulates in glial cells as tufted astrocytes and coiled bodies can be numerous in diencephalon and rostral brainstem. In CBD, astrocytic plaques with tau-positive clusters in distal processes are

[1]*Queen Square Brain Bank for Neurological Disorders, UCL Institute of Neurology, University College London, London, UK;* [2]*Sobell Department of Motor Neuroscience and Movement Disorders, University College London, London, UK*

***Correspondence to**: Dr. Helen Ling, Reta Lila Weston Institute of Neurological Studies, 1 Wakefield Street, UCL Institute of Neurology, London WC1N 1PJ, United Kingdom; E-mail: h.ling@ucl.ac.uk*

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pathognomonic and coiled bodies are less frequent and mainly observed in white matter. Tufted astrocytes and astrocytic plaques are the pathological hallmarks for PSP and CBD, respectively. These tau-positive glial lesions have different morphology and they do not appear to coexist in the same brain.

Tau Biochemical Fingerprints

Six tau isoforms are expressed by alternative mRNA splicing of exons 2, 3, and 10 of the MAPT gene located on chromosome 17.[10] The extra repeat domain, which is expressed in 4R tau, is coded by exon 10 of MAPT. Tau filaments in PSP and CBD are made up of predominantly 4R tau. Western blots of insoluble filamentous tau extracted from affected brain regions of PSP and CBD show two major bands of 68 and 64 kDa, made of hyperphosphorylated 4R tau isoforms. In contrast, three major bands of 60, 64, and 68 kDa are detected in Alzheimer's disease representing a mixture of 3R and 4R tau.

PSP and CBD are collectively categorised as 4R-tauopathy in the modern molecular classification of frontotemporal lobar degeneration (FTLD-tau).[11] Nevertheless, PSP and CBD have distinct biochemical fingerprints as demonstrated by different lower molecular weight proteolytic tau fragments on Western blots; a 33kDa band in PSP and two closely related bands of approximately 37kDa in CBD.[12] A recent study of oligodendroglial cytoplasmic tau inclusions in the form of coiled bodies showed distinct ultrastructural and biochemical characteristics distinguishing CBD from PSP.[13]

Tau Genetics

More than 50 pathogenic mutations of the MAPT gene have been identified.[14] These autosomal dominant tau mutations cause an inherited form of frontotemporal dementia with parkinsonism, which is now collectively classified as FTDP-17T.[14] Their discovery established the causal relationship between tau dysfunction and neurodegeneration and the clinical manifestation of cognitive and motor impairments.

In FTDP-17T, abnormal accumulation of tau can occur in neurons or in both neurons and glia. The clinical presentations, cell types, and morphology of tau-positive inclusions vary according to the nature and location of MAPT gene mutations. A mutation may lead to a structurally abnormal protein, an abnormal 3R to 4R ratio, or both. As a result, tau becomes hyper-phosphorylated and assembles into insoluble filamentous tau, causing dysfunction and death of nerve cells through a pathological pathway, which is still not clearly understood but is central to the neurodegenerative process in FTDP-17T.

Although the majority of PSP and CBD cases are sporadic, certain MAPT mutations can result in clinical phenotypes and pathological features that are indistinguishable from PSP or CBD and may be considered as the monogenetic causes of PSP and CBD.[14] The genetic-pathological correlations demonstrated by these FTDP-17T cases serve as strong evidence of the fundamental mechanistic difference between PSP and CBD. The assessment of clinical and family history, genetic tests, and in postmortem cases, neuropathological characterization is necessary to distinguish FTDP-17T from sporadic PSP or CBD.

Clinical Heterogeneity and Vulnerable Neural Network

RS and CBS are the classic clinical phenotypes of PSP and CBD, respectively. The RS phenotype is observed in more than half of PSP cases. Other main clinical phenotypes of PSP are parkinsonism subtype (PSP-P), pure akinesia with gait freezing (PSP-PAGF, or progressive gait freezing, PSP-PGF), corticobasal syndrome (PSP-CBS), primary non-fluent aphasia (PSP-PNFA, speech or language disorder, PSP-SL), behavioral variant frontotemporal dementia (PSP-bvFTD, or predominant frontal presentation, PSP-F), and cerebellar ataxia (PSP-C).[4,15] CBS is the clinical presentation in 25 to 50% of autopsy-confirmed CBD cases.[2,6] Other well described clinical phenotypes are CBD-RS, CBD-bvFTD, CBD-PNFA and posterior cortical atrophy (CBD-PCA).[16] The latest CBD clinical diagnostic criteria allocated four major CBD phenotypes into CBS, PSP syndrome (PSPS), frontal behavioral-spatial syndrome (FBS), and nonfluent/agrammatic variant of primary progressive aphasia (naPPA).[17] Clinical features of two phenotypes may also be observed in one individual, such as vertical supranuclear gaze palsy and asymmetrical limb apraxia.

Clinico-pathological studies have demonstrated the association between clinical phenotypes and the severity and topographic distribution of tau pathology and neuronal loss.[2,18] For instance, a shift in tau burden from the deep gray structures to the cortical regions was demonstrated in PSP-CBS cases when compared with PSP-RS.[2] This quantitative pathological finding correlates with the cortical clinical features in PSP-CBS.

Heterogeneous clinical phenotypes linked with PSP and CBD represent the pathological involvement of the behavioral, cognitive, primary motor, and extrapyramidal pathways.[19] The concept of "molecular nexopathies" proposes that pathological proteins target specific neural networks leading to phenotypic variation.[20] In PSP and CBD, tau oligomers are considered responsible for the spread of tau pathology through the brain as the disease advances.[21] "Tau strains" are likely to differ between PSP and CBD, explaining their distinct classic clinical phenotypes, a result of the dysfunction of susceptible neural networks targeted by specific tau strains.[22] Concomitant pathological proteins such as TDP-43 may play similar role in influencing network susceptibility and clinical presentation. Other proposed factors contributing to neural network susceptibility involve genetic, epigenetic, and environmental interactions.[19]

Prion-like Propagation and Tau Strains

Animal studies demonstrated that intracerebral injection of brain homogenates from humans with autopsy-confirmed PSP and CBD produced distinct tau lesions in mouse brains reminiscent of

TABLE 1 Key Differences at Multiple Levels Between PSP and CBD

Neuropathological features	PSP and CBD have their own validated neuropathological diagnostic criteria and are considered as distinct pathological entities.[8,9] The overall patterns of distribution of neuronal and glial lesions are different.[7]
Tau biochemistry	PSP and CBD have distinct biochemical fingerprints as demonstrated by different lower molecular weight proteolytic tau fragments on Western blots.[12]
Tau genetics	Specific MAPT mutations are associated with pathological signatures of PSP and CBD indicating distinct mechanistic differences between PSP and CBD.
Classic clinical phenotypes	Their distinct classic clinical phenotypes of PSP and CBD are likely a result of the dysfunction of susceptible neural networks targeted by specific tau strains.[22]
Prion-like propagation	Intracerebral injection of brain homogenates from humans with autopsy-confirmed PSP and CBD produced distinct tau lesions in mouse brains likened to those of the respective human tauopathies,[22–24] suggesting PSP and CBD have different underlying pathological processes.[25,26]

the hallmarks of the respective human tauopathies (i.e., tufted astrocytes in PSP and astrocytic plaques in CBD).[22–24] The injection of brain homogenates does not only induce the formation of tau inclusions at the injection sites but also leads to their subsequent spread to distant brain regions connected by specific neural networks, which vary between tauopathies.[22–24] These findings support the notion that PSP and CBD have distinct tau strains and represent different pathological processes.[25,26]

A "prion-like" templating mechanism is central to tau propagation and disease progression.[24,26] The term "prion-like" refers to the release of protein aggregates from a small number of neurons to the extracellular space and their uptake by neurons in other connected brain regions, followed by the initiation of a self-amplifying cascade. Aggregation inhibitors and antibodies targeting extracellular tau aggregates are potential therapeutic targets to impede tau-induced seeding and spreading.[10]

Conclusions

PSP and CBD are closely related but different disorders that demonstrate distinct pathological signature, biochemical, and ultrastructural fingerprints and most likely possess different tau strains, which in turn target specific susceptible neural networks.

Continued effort is necessary to investigate the earliest brain regions involved in tau seeding and the mechanistic pathways from tau aggregation and propagation to neuronal dysfunction and cell death.[27] The answers to these questions hold the key to the development of antemortem diagnostic biomarkers and effective mechanistic-based therapy.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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